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14. ABSTRACT

This study examines the efficacy of two cognitive-behavioral treatments for PTSD-related recurrent nightmares and other sleep difficulties in veterans of Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) in a randomized controlled trial. Participants will be 160 OEF/OIF veterans presently in outpatient treatment for PTSD at one of two study sites, the Philadelphia VAMC or the VACHS, West Haven, CT.

During Year One of this award, the study procedures received approval by four regulatory bodies (PVAMC IRB, VACHS IRB, Yale University IRB and DoD HRPO). Data collection is currently ongoing at the Philadelphia site. Data will be analyzed at the end of the data collection period and therefore research findings are not yet available.

15. SUBJECT TERMS
Posttraumatic Stress Disorder, Nightmares, Randomized Controlled Trial, Cognitive-behavioral Treatment, OEF/OIF Veterans

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Section I: Introduction

A substantial proportion of Veterans returning from Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) have significant psychological symptoms related to traumatic war zone exposure, including recurrent nightmares and other sleep disturbances. Nightmares are generally distressing and difficult to treat, often persisting despite successful resolution of other Posttraumatic Stress Disorder (PTSD) symptoms. A cognitive-behavioral treatment (CBT), Imagery Rehearsal (IR), appears to have promise for successfully treating nightmares. This study investigates the efficacy of IR in treating OEF/OIF veterans, many of whom likely have mild to moderate traumatic brain injury (TBI). There are three main objectives of this study: 1) to examine the efficacy of IR, combined with psychoeducation about PTSD and nightmares and standard CBT for insomnia (IR + PPCI), compared to psychoeducation about PTSD and nightmares and CBT for insomnia (PPCI) alone, in reducing nightmare frequency and improving global sleep quality in OEF/OIF veterans with PTSD; 2) to determine whether there are moderating effects of neurocognitive impairment on the efficacy of these two forms of CBT for nightmares; and 3) to explore possible neurobiological correlates of treatment-related changes in nightmare frequency and sleep quality, focusing on noradrenergic systems. One hundred and sixty OEF/OIF veterans enrolled in treatment for PTSD at the Philadelphia VA Medical Center (PVAMC) or the VA Connecticut Health Care System (VACHS), West Haven Campus, will be randomized to one of two individual treatments: IR + PPCI or PPCI alone. Participants are referred by their mental health treatment providers and assessed for PTSD and war zone-related nightmares. Participants complete a battery of computerized neuropsychological tests at baseline and are stratified in their randomization to either group depending on the results. Once randomized, participants meet for 6 weekly individual sessions of IR + PPCI or PPCI alone. Participants complete self-report questionnaires assessing nightmares, sleep quality, PTSD, and depression, at baseline, immediately after treatment, and again three and six months after treatment. Additionally, participants provide saliva samples for measurement of salivary alpha-amylase, a marker of peripheral noradrenergic activity, both before sleep onset and upon awakening, for two nights before treatment and for two nights before the first post-treatment assessment.

Section II: Progress to Date on 5 Study Tasks in Approved Statement of Work:

1. Obtaining approvals for the study protocol at the study locations.

A. Philadelphia VAMC/University of Pennsylvania:

- Regulatory review of the initial protocol was completed by the PVAMC IRB on 3/13/2008 and the DoD HRPO on 2/13/2009. During the current reporting year, we have submitted the following amendments to this protocol: Addition of PVAMC-affiliated community-based outpatient clinics (CBOCs in Camden, NJ; Gloucester, NJ; Horsham, PA, and Fort Dix, NJ) around Philadelphia as recruitment sites (8/24/10); Research staff form: Jacqueline Halpern, assessor, added (9/22/10); Letter to providers; Referral process at CBOCs (11/23/10);

Staff form: Dr. Subhajit Chakravorty, clinical monitor, added (12/23/10); Protocol: change clinical monitor, referral forms for CBOCs, incl./excl. check-list (12/23/10); Referral form for Gloucester CBOC (2/8/11)

B. VACHS, West Haven/Yale University:

- Regulatory review of the initial protocol was completed by the VACHS IRB and Research and Development Committee on 6/5/2008 and by the Yale University IRB on 11/12/2008. The DoD HRPO approved this protocol on 2/24/2009. The following amendment was submitted to this protocol during the current reporting period: Closure of recruitment at VACHS site (12/1/10).

- **PROBLEMS ENCOUNTERED:**
  Delay in closure of secondary site: There was a delay in the submission of the amendment describing recruitment closure at the VACHS site. An IRB audit at the Philadelphia site alerted the VACHS site PI to the need to submit an amendment to notify the VACHS and Yale IRBs that the site is closed to recruitment.

2. Recruitment, assessment and randomization of 80 participants at the PVAMC site and 80 at the VACHS site (total N=160).

A. Philadelphia VAMC:

- The PVAMC site was the source of 35 referrals from treatment providers during the reporting period. Eighty percent (28) were male, and 20% (7) were female. Thirty-seven percent (13) were African-American, 17% (6) Hispanic, and 46% (16) Caucasian. Assessments were scheduled with 14 potential participants: 10 Veterans completed both assessment sessions, and all were enrolled in the study: four were randomized to IR + PPCI and six to PPCI alone.
- The Philadelphia VAMC-affiliated CBOCs were the source of 76 referrals from treatment providers during the reporting period. Ninety percent (68) were male, and 10% (8) were female. Approximately eighteen percent (14) were African-American, 11% (8) Hispanic, 53% (40) Caucasian, 3% (2) American Indian/Alaskan Native, and 16% (12) of other ethnic background. Assessments were scheduled with 16 potential participants: 16 completed the first assessment, and 14 Veterans completed the second assessment as well. Thirteen participants were enrolled in the treatment study in the past year: six were randomized to IR + PPCI and seven to PPCI alone.
- **PROBLEMS ENCOUNTERED:**
  - Technical issues: Due to problems with the interface between research, IT and statistical aspects of this project, we had to restart the development of the study database using a different statistical package. In collaboration with study statisticians, this project was completed, and we have a working database; data entry has begun and will be ongoing.

- Start up at the PVAMC-affiliated community-based outpatient clinics (CBOCs): During this reporting period, we expanded our recruitment sites to include the four PVAMC-affiliated CBOCs around Philadelphia. This promising expansion of the Philadelphia site resulted in the need for additional personnel: we hired a full- time traveling assessor to aid in recruitment and assessment of CBOC patients, and we identified and trained three new psychologists at three of the four CBOCs to deliver study treatments in those locations; the study co-PI, Dr. G. Harb, is delivering the treatments at the fourth CBOC. The process of setting up at the CBOCs was complicated by the need for computer equipment and access to the VA network for the assessor, who administers a specialized computerized neuropsychological assessment to participants at the beginning of their involvement with the study. We succeeded in obtaining a government-issued laptop, having internet ports activated, and having computer programs installed at most sites. The one site that remains problematic with regard to computer issues is the Ft. Dix site, and we are working on increasing the consistency of the internet connection needed for the assessment. We continue to work with IT personnel at Ft. Dix as well as the computerized program's developers at the University of Pennsylvania to arrive at an optimal solution.

- Recruitment challenges: As many other investigators (and VA clinicians) across the country have reported, we have faced difficulties recruiting and retaining participants. We have taken many measures at the PVAMC to increase recruitment, such as doing outreach to different departments (including the Post-deployment Clinic, the Polytrauma team, the Women's Clinic, the Sleep Center, and the Neurology Service), adjusting our inclusion/exclusion criteria (e.g. to allow for alcohol abuse), and obtaining approval to proactively scan computer schedules for upcoming appointments of potential participants. However, our most recent change in procedure, our outreach to the PVAMC-affiliated CBOCs, appears to be the most successful strategy. Since recruitment at these facilities began, we have, on average, enrolled slightly over 2 Veterans at the CBOCs per month, and one at the PVAMC per month (see Table 1, below). It appears that OEF/OIF Veterans are more likely to seek treatment outside the city and closer to their homes; parking is available, traffic is not too stressful, and negotiating a major medical center is not required. Although it remains true that this younger group of Veterans is often ambivalent about treatment, and that they have many other life responsibilities that may preclude consistent attendance at treatment sessions, we are hopeful that this strategy will continue to increase recruitment into the future**.** At the current rate of 3 new Veterans enrolled per month, we would be able to recruit approximately 36 participants per year.

Table 1: Recruitment at PVAMC and affiliated CBOCs

Recruitment Site	Recruitment Start Date	Referred	Assessed	Enrolled PPCI+IR	Enrolled PPCI
Willow Grove CBOC	November 2010	21	4	2	1
Camden CBOC	November 2010	17	4	2	1
Gloucester CBOC	January 2011	20	4	2	2
Ft.Dix CBOC	March 2011	18	4	2	1
PVAMC	All year	35	14	4	6

B. VACHS, West Haven:

- The VACHS site received 22 referrals from treatment providers and 14 self-referrals, of which 89% were male and 11 % were female, with an average age of 35. Fifty-eight and three tenths percent were Caucasian, 22.2% African-American, and 19.4% Hispanic/Latino. Assessments were scheduled with 12 potential participants, and six Veterans completed the second assessment. Six participants were enrolled in the treatment study.
- The VACHS site has been closed to enrollment since 4/2010.

3. Administration of six sessions of the protocol treatments to participants.

A. Philadelphia VAMC:

- At the PVAMC, of the ten Veterans enrolled at this site this year, six have completed all six sessions of treatment and are in the follow-up phase, one has completed all follow-up visits, two are currently in treatment, and one Veteran has withdrawn from the study.
- At the CBOCs, of the 13 Veterans enrolled at these sites this year, seven have completed all six sessions of treatment and are in the follow-up phase, five are currently in treatment, and one has withdrawn from the study.
- Treatment fidelity: During Year One of this award, a detailed supervision plan as well as fidelity rating procedures were developed, and these are being used. Weekly supervision calls with study supervisors, Drs. Philip Gehrman and Andrea Phelps, are attended by all therapists and have ensured treatment protocol adherence across sites.

B. VACHS, West Haven:

- Of the six participants enrolled in the treatment study over the course of VACHS' participation, one Veteran withdrew after completing one session of treatment. Five Veterans completed the treatment and all follow-up assessments.

4. Follow-up: re-assessment for detection of treatment effects and maintenance of benefits immediately post-treatment, and at 3 months and 6 months post-treatment.

A. Philadelphia VAMC:

- At the PVAMC, six Veterans are currently active in the follow-up phase of the study, and one Veteran completed all study follow-ups. Of the six in follow-up, all have completed the first post-treatment assessment and the 3-month follow-up, and two have completed the 6-month follow-up. We have lost no Veterans to follow-up this year.
- At the CBOCs, seven Veterans are currently in the follow-up phase of the study. All seven have completed the first post-treatment follow-up, three have completed the 3-month follow-up, and none have completed the 6-month follow-up. We have lost no Veterans to follow-up this year.

B. VACHS, West Haven:

- Five participants completed all post-treatment and follow-up assessments as of December 2010.
- No Veterans remain actively enrolled in this study at VACHS.

5. Statistical analysis of the data and manuscript preparation.

- The project is in the data collection phase, and no statistical analyses currently are being done.

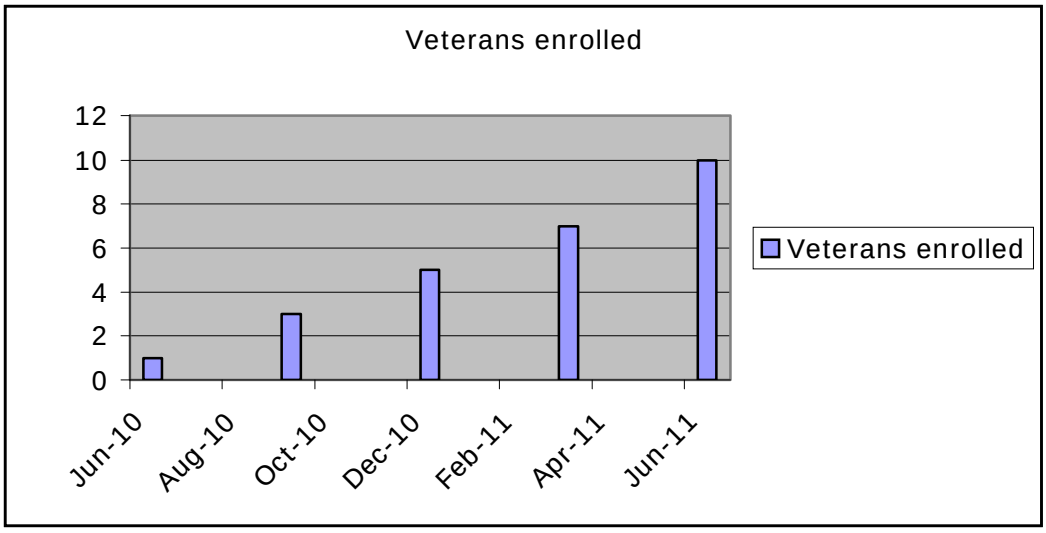
Philadelphia VAMC:

- Entry of data from assessed and enrolled participants is ongoing at the PVAMC and its affiliated CBOCs.
- Data from the closed VACHS site is still in the process of being transferred to the PVAMC.

Section III: Key Research Accomplishments:

- Completion of lengthy regulatory reviews at PVAMC, Yale University, VACHS, as well as the DOD HRPO.
- Hiring and training of staff, most recently new staff to recruit, assess, and provide treatment at the PVAMC-affiliated CBOCs.
- Participant recruitment is ongoing at the PVAMC site and its affiliated CBOCs.
- Extensive efforts to boost recruitment rates; this has involved making necessary modifications to study protocols.
- Successful shift of recruitment from the VACHS site, which discontinued recruitment of participants for the study in April 2010, to the PVAMC-affiliated CBOCs.
- Successful increase in recruitment rates, see Figure 1, below.

Figure 1. Number of Veterans enrolled during the reporting period



Section IV: Reportable Outcomes: Presentations:
None

Section V: Conclusions:
During this contract period, only the primary site in Philadelphia has actively recruited participants. In order to most efficiently conclude this project, we shifted recruitment from the VACHS site entirely to Philadelphia. This necessitated an expansion of the Philadelphia site, to include the four community based outpatient clinics around Philadelphia (Camden, NJ; Gloucester, NJ; Ft. Dix, NJ; and Willow Grove, PA). We hired new staff, solved most IT difficulties, and began recruitment in December of 2010. Recruitment at the CBOCs has been a very promising addition to our study protocol.

In total, we enrolled 23 participants during the reporting year, with 13 participants currently in the follow-up phase of the study. Of these 23, 13 were enrolled at the CBOCs, showing the value of reaching out to these outpatient clinics. We are currently on track to enroll over 30 participants per year with this new recruitment strategy. Due to the prior difficulties with delayed project start-up due to lengthy approval processes by four different oversight agencies (IRBs and HRPO) and due to the difficulty with recruitment in this particular study population, our study progress was delayed. In addition, the loss of a recruitment site and the creation of this new recruitment strategy have further delayed recruitment to meet our project goal. We therefore will apply for a no-cost extension of the project to enable us to enroll the projected number of participants and to conclude the project in a scientifically sound manner.

In addition, our project statistician has examined the power of the study to detect clinically meaningful effects if a smaller number of participants than originally planned were ultimately enrolled in this study. With a two-year no cost extension, data collection could continue through Year Four and one additional year (with another year for data analysis). Using our current recruitment rate of three Veterans per month, we could

accrue approximately 115 participants at the close of enrollment. To estimate the loss in statistical power from a reduction in the sample of subjects from 150 to 115, our current estimate of the number of accrued participants with such an extension, we performed statistical power simulations using the same simulation programs and same assumptions as in the original submission. For the same detectable treatment effect (about 1/2 of a standard deviation) as with an estimated sample of 150, the statistical power drops from 0.84 to 0.70. However, with 115 patients, there remains good power (0.96) to detect a 1/3 standard deviation in relative improvement in PSQI score time in the treatment group. Thus, even with a slower than planned accrual, the study as originally designed should have good power to detect a clinically meaningful treatment effect.